‘rstanguts’: Bayesian inference of GUTS models with R using Stan language

Virgile Baudrot[1] **and Sandrine Charles**[1]

[1]**UMR CNRS 5558 LBBE, Université Lyon 1, 43 Boulevard du 11 Novembre 1918, 69100 Villeurbanne**

Corresponding author:
Virgile Baudrot[1]

Email address: virgile.baudrot@posteo.net

ABSTRACT

The toxicokinetic-toxicodynamic (TKTD) modeling approach proved to be of particular interest in strengthening the Environmental Risk Assessment (ERA) of chemicals compounds. TKTD models describe the time-course of processes leading to toxicity at the level of organisms. These models may include all mechanisms from the toxicokinetics part describing the compound fate from external concentration to internal kinetics (e.g., exposure, uptake, elimination, biotransformation, internal distribution), and translate the internal concentration into toxicodynamics covering alteration of cells and organs functioning that can eventually lead to a toxic effect at the organism level (e.g., mortality, reduced reproduction, abnormal behavior) then affecting the population dynamic. While an integrative mathematical framework as GUTS offers an efficient theoretical approach, its practical use for parameter estimation is challenging (from model implementation to parameter estimation), especially with time-variable exposure. Faced with this difficulty, Bayesian approach for GUTS models has multiple advantages as (i) using all data provided by the experiments, (ii) taking into account the knowledge from experts and/or previous studies, (iii) being still relevant for complex model with small data set, and (iv) handling uncertainties by providing distributions of parameter posteriors. To facilitate the access to Bayesian fitting of GUTS models based on ordinary differential equations, we implemented GUTS models within R using the the Stan language dedicated to Bayesian statistics. In this paper, we compare the result of models implementation (goodness-of-fit and speedups) and provided some guidelines for using Bayesian approach in ecotoxicology. For survival analysis of organisms in response to a chemical stressor, the General Unified Threshold model of Survival (GUTS) is today recognized as a suitable and powerful TKTD framework incorporating two complimentary death mechanisms: Stochastic Death (GUTS-SD) and Individual Tolerance (GUTS-IT), from which a large range of existing models can be derived.

INTRODUCTION

References: (Vehtari, Gelman, and Gabry 2017), (Carpenter et al. 2017)

MATHEMATICAL DESCRIPTION OF GUTS MODELS

References to look at: (Jager and Ashauer 2018), (Jager et al. 2011), (Delignette-Muller, Ruiz, and Veber 2017), (Baudrot, Preux, et al. 2018)

1 IMPLEMENTATION OF ‘RSTANGUTS’

References to look at: (Delignette-Muller, Ruiz, and Veber 2017), (Baudrot, Preux, et al. 2018), (Baudrot, Charles, et al. 2018)

The implementation was done using the *rstantools* package (Gabry and Goodrich 2017).

2 PRACTICAL APPLICATION EXAMPLE

The package `rstanguts` is devoted to the analysis of data from standard toxicity tests. It provides a simple workflow to calibrate GUTS models. In this section, we illustrate a typical use of `rstanguts` on

Figure 1. An example image.

survival data, which can be followed step-by-step to analyze new datasets as it is also described in the vignette `getting-started`.

In the following example, we use a classical data set of *Gammarus pulex* exposed to diazinon (Ashauer et al. 2010) as used in the R package *GUTS* from Albert, Vogel, and Ashauer (2016; Albert and Vogel 2017). This data set is already in the package, so you can have access to the data simply by using the `data()` function.

HELP TO WRITE THE MANUSCRIPT

Some LaTeX Examples

Use section and subsection commands to organize your document. LaTeX handles all the formatting and numbering automatically. Use ref and label commands for cross-references.

Figures and Tables

Use the table and tabular commands for basic tables — see Table @ref(tab:widgets), for example. You can upload a figure (JPEG, PNG or PDF) using the project menu. To include it in your document, use the includegraphics command as in the code for Figure @ref(fig:view) below.

Standard LaTeXreferences will work as well (e.g. Fig. 1).

Table 1. (#tab:widgets) An Example Table.

Item	Quantity
Widgets	42
Gadgets	13

Mathematics

LaTeX is great at typesetting mathematics. Let $X_1, X_2, \ldots, X_n$ be a sequence of independent and identically distributed random variables with $\mathrm{E}[X_i] = \mu$ and $\mathrm{Var}[X_i] = \sigma^2 < \infty$, and let

$$S_n = \frac{X_1 + X_2 + \cdots + X_n}{n} = \frac{1}{n}\sum_{i}^{n} X_i$$

denote their mean. Then as n approaches infinity, the random variables $\sqrt{n}(S_n - \mu)$ converge in distribution to a normal $\mathcal{N}(0, \sigma^2)$.

Lists

You can make lists with automatic numbering ...

1. Like this,
2. and like this.

METHODS

Quisque ullamcorper placerat ipsum. Cras nibh. Morbi vel justo vitae lacus tincidunt ultrices. Lorem ipsum dolor sit amet, consectetuer adipiscing elit. In hac habitasse platea dictumst. Integer tempus convallis augue. Etiam facilisis. Nunc elementum fermentum wisi. Aenean placerat. Ut imperdiet, enim sed gravida sollicitudin, felis odio placerat quam, ac pulvinar elit purus eget enim. Nunc vitae tortor. Proin tempus nibh sit amet nisl. Vivamus quis tortor vitae risus porta vehicula.

$$\cos^3\theta = \frac{1}{4}\cos\theta + \frac{3}{4}\cos 3\theta \tag{1}$$

Fusce mauris. Vestibulum luctus nibh at lectus. Sed bibendum, nulla a faucibus semper, leo velit ultricies tellus, ac venenatis arcu wisi vel nisl. Vestibulum diam. Aliquam pellentesque, augue quis sagittis posuere, turpis lacus congue quam, in hendrerit risus eros eget felis. Maecenas eget erat in sapien mattis porttitor. Vestibulum porttitor. Nulla facilisi. Sed a turpis eu lacus commodo facilisis. Morbi fringilla, wisi in dignissim interdum, justo lectus sagittis dui, et vehicula libero dui cursus dui. Mauris tempor ligula sed lacus. Duis cursus enim ut augue. Cras ac magna. Cras nulla. Nulla egestas. Curabitur a leo. Quisque egestas wisi eget nunc. Nam feugiat lacus vel est. Curabitur consectetuer.

Subsection

Suspendisse vel felis. Ut lorem lorem, interdum eu, tincidunt sit amet, laoreet vitae, arcu. Aenean faucibus pede eu ante. Praesent enim elit, rutrum at, molestie non, nonummy vel, nisl. Ut lectus eros, malesuada sit amet, fermentum eu, sodales cursus, magna. Donec eu purus. Quisque vehicula, urna sed ultricies auctor, pede lorem egestas dui, et convallis elit erat sed nulla. Donec luctus. Curabitur et nunc. Aliquam dolor odio, commodo pretium, ultricies non, pharetra in, velit. Integer arcu est, nonummy in, fermentum faucibus, egestas vel, odio.

Paragraph Sed commodo posuere pede. Mauris ut est. Ut quis purus. Sed ac odio. Sed vehicula hendrerit sem. Duis non odio. Morbi ut dui. Sed accumsan risus eget odio. In hac habitasse platea dictumst. Pellentesque non elit. Fusce sed justo eu urna porta tincidunt. Mauris felis odio, sollicitudin sed, volutpat a, ornare ac, erat. Morbi quis dolor. Donec pellentesque, erat ac sagittis semper, nunc dui lobortis purus, quis congue purus metus ultricies tellus. Proin et quam. Class aptent taciti sociosqu ad litora torquent per conubia nostra, per inceptos hymenaeos. Praesent sapien turpis, fermentum vel, eleifend faucibus, vehicula eu, lacus.

Paragraph Pellentesque habitant morbi tristique senectus et netus et malesuada fames ac turpis egestas. Donec odio elit, dictum in, hendrerit sit amet, egestas sed, leo. Praesent feugiat sapien aliquet odio. Integer vitae justo. Aliquam vestibulum fringilla lorem. Sed neque lectus, consectetuer at, consectetuer sed, eleifend ac, lectus. Nulla facilisi. Pellentesque eget lectus. Proin eu metus. Sed porttitor. In hac habitasse platea dictumst. Suspendisse eu lectus. Ut mi mi, lacinia sit amet, placerat et, mollis vitae, dui. Sed ante tellus, tristique ut, iaculis eu, malesuada ac, dui. Mauris nibh leo, facilisis non, adipiscing quis, ultrices a, dui.

Subsection

Morbi luctus, wisi viverra faucibus pretium, nibh est placerat odio, nec commodo wisi enim eget quam. Quisque libero justo, consectetuer a, feugiat vitae, porttitor eu, libero. Suspendisse sed mauris vitae elit sollicitudin malesuada. Maecenas ultricies eros sit amet ante. Ut venenatis velit. Maecenas sed mi eget dui varius euismod. Phasellus aliquet volutpat odio. Vestibulum ante ipsum primis in faucibus orci luctus et ultrices posuere cubilia Curae; Pellentesque sit amet pede ac sem eleifend consectetuer. Nullam elementum, urna vel imperdiet sodales, elit ipsum pharetra ligula, ac pretium ante justo a nulla. Curabitur tristique arcu eu metus. Vestibulum lectus. Proin mauris. Proin eu nunc eu urna hendrerit faucibus. Aliquam auctor, pede consequat laoreet varius, eros tellus scelerisque quam, pellentesque hendrerit ipsum dolor sed augue. Nulla nec lacus.

Reference to Figure @ref(fig:results).

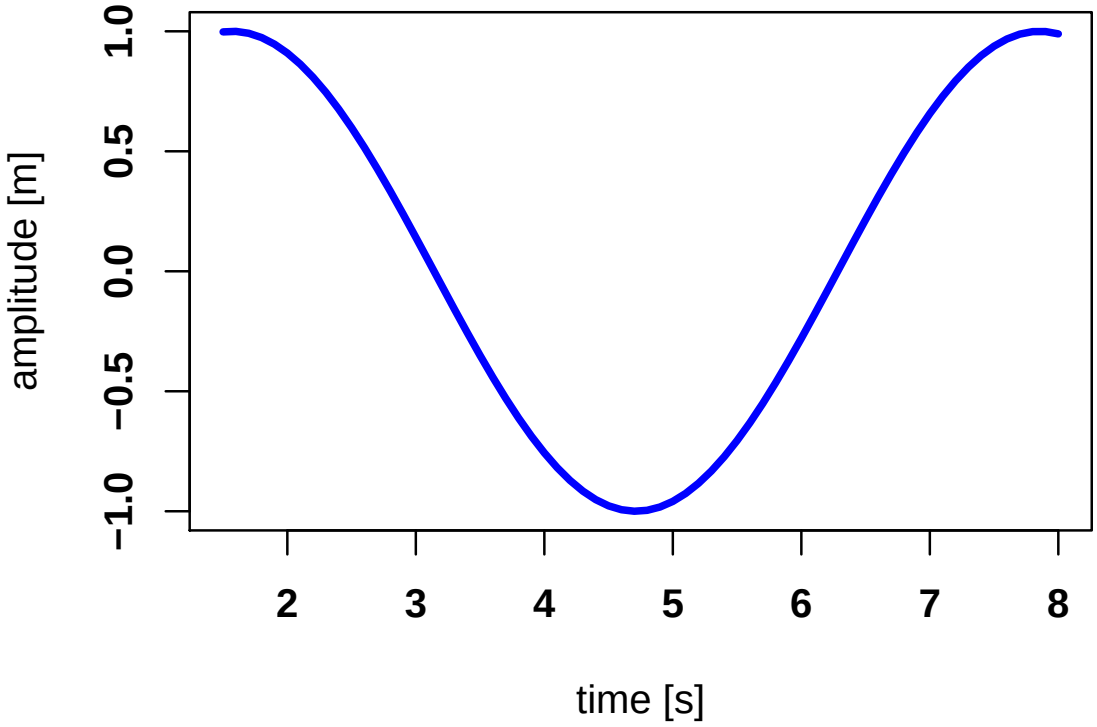

Figure 2. In-text Picture

RESULTS AND DISCUSSION

Suspendisse vitae elit. Aliquam arcu neque, ornare in, ullamcorper quis, commodo eu, libero. Fusce sagittis erat at erat tristique mollis. Maecenas sapien libero, molestie et, lobortis in, sodales eget, dui. Morbi ultrices rutrum lorem. Nam elementum ullamcorper leo. Morbi dui. Aliquam sagittis. Nunc placerat. Pellentesque tristique sodales est. Maecenas imperdiet lacinia velit. Cras non urna. Morbi eros pede, suscipit ac, varius vel, egestas non, eros. Praesent malesuada, diam id pretium elementum, eros sem dictum tortor, vel consectetuer odio sem sed wisi.

Subsection

Sed feugiat. Cum sociis natoque penatibus et magnis dis parturient montes, nascetur ridiculus mus. Ut pellentesque augue sed urna. Vestibulum diam eros, fringilla et, consectetuer eu, nonummy id, sapien. Nullam at lectus. In sagittis ultrices mauris. Curabitur malesuada erat sit amet massa. Fusce blandit. Aliquam erat volutpat. Aliquam euismod. Aenean vel lectus. Nunc imperdiet justo nec dolor.

Subsubsection

Etiam euismod. Fusce facilisis lacinia dui. Suspendisse potenti. In mi erat, cursus id, nonummy sed, ullamcorper eget, sapien. Praesent pretium, magna in eleifend egestas, pede pede pretium lorem, quis consectetuer tortor sapien facilisis magna. Mauris quis magna varius nulla scelerisque imperdiet. Aliquam non quam. Aliquam porttitor quam a lacus. Praesent vel arcu ut tortor cursus volutpat. In vitae pede quis diam bibendum placerat. Fusce elementum convallis neque. Sed dolor orci, scelerisque ac, dapibus nec, ultricies ut, mi. Duis nec dui quis leo sagittis commodo.

Subsubsection

Etiam ac leo a risus tristique nonummy. Donec dignissim tincidunt nulla. Vestibulum rhoncus molestie odio. Sed lobortis, justo et pretium lobortis, mauris turpis condimentum augue, nec ultricies nibh arcu pretium enim. Nunc purus neque, placerat id, imperdiet sed, pellentesque nec, nisl. Vestibulum imperdiet neque non sem accumsan laoreet. In hac habitasse platea dictumst. Etiam condimentum facilisis libero. Suspendisse in elit quis nisl aliquam dapibus. Pellentesque auctor sapien. Sed egestas sapien nec lectus. Pellentesque vel dui vel neque bibendum viverra. Aliquam porttitor nisl nec pede. Proin mattis libero vel

turpis. Donec rutrum mauris et libero. Proin euismod porta felis. Nam lobortis, metus quis elementum commodo, nunc lectus elementum mauris, eget vulputate ligula tellus eu neque. Vivamus eu dolor.

Subsection

Nulla in ipsum. Praesent eros nulla, congue vitae, euismod ut, commodo a, wisi. Pellentesque habitant morbi tristique senectus et netus et malesuada fames ac turpis egestas. Aenean nonummy magna non leo. Sed felis erat, ullamcorper in, dictum non, ultricies ut, lectus. Proin vel arcu a odio lobortis euismod. Vestibulum ante ipsum primis in faucibus orci luctus et ultrices posuere cubilia Curae; Proin ut est. Aliquam odio. Pellentesque massa turpis, cursus eu, euismod nec, tempor congue, nulla. Duis viverra gravida mauris. Cras tincidunt. Curabitur eros ligula, varius ut, pulvinar in, cursus faucibus, augue.

Nulla mattis luctus nulla. Duis commodo velit at leo. Aliquam vulputate magna et leo. Nam vestibulum ullamcorper leo. Vestibulum condimentum rutrum mauris. Donec id mauris. Morbi molestie justo et pede. Vivamus eget turpis sed nisl cursus tempor. Curabitur mollis sapien condimentum nunc. In wisi nisl, malesuada at, dignissim sit amet, lobortis in, odio. Aenean consequat arcu a ante. Pellentesque porta elit sit amet orci. Etiam at turpis nec elit ultricies imperdiet. Nulla facilisi. In hac habitasse platea dictumst. Suspendisse viverra aliquam risus. Nullam pede justo, molestie nonummy, scelerisque eu, facilisis vel, arcu.

Curabitur tellus magna, porttitor a, commodo a, commodo in, tortor. Donec interdum. Praesent scelerisque. Maecenas posuere sodales odio. Vivamus metus lacus, varius quis, imperdiet quis, rhoncus a, turpis. Etiam ligula arcu, elementum a, venenatis quis, sollicitudin sed, metus. Donec nunc pede, tincidunt in, venenatis vitae, faucibus vel, nibh. Pellentesque wisi. Nullam malesuada. Morbi ut tellus ut pede tincidunt porta. Lorem ipsum dolor sit amet, consectetuer adipiscing elit. Etiam congue neque id dolor.

Donec et nisl at wisi luctus bibendum. Nam interdum tellus ac libero. Sed sem justo, laoreet vitae, fringilla at, adipiscing ut, nibh. Maecenas non sem quis tortor eleifend fermentum. Etiam id tortor ac mauris porta vulputate. Integer porta neque vitae massa. Maecenas tempus libero a libero posuere dictum. Vestibulum ante ipsum primis in faucibus orci luctus et ultrices posuere cubilia Curae; Aenean quis mauris sed elit commodo placerat. Class aptent taciti sociosqu ad litora torquent per conubia nostra, per inceptos hymenaeos. Vivamus rhoncus tincidunt libero. Etiam elementum pretium justo. Vivamus est. Morbi a tellus eget pede tristique commodo. Nulla nisl. Vestibulum sed nisl eu sapien cursus rutrum.

Nulla non mauris vitae wisi posuere convallis. Sed eu nulla nec eros scelerisque pharetra. Nullam varius. Etiam dignissim elementum metus. Vestibulum faucibus, metus sit amet mattis rhoncus, sapien dui laoreet odio, nec ultricies nibh augue a enim. Fusce in ligula. Quisque at magna et nulla commodo consequat. Proin accumsan imperdiet sem. Nunc porta. Donec feugiat mi at justo. Phasellus facilisis ipsum quis ante. In ac elit eget ipsum pharetra faucibus. Maecenas viverra nulla in massa.

Nulla ac nisl. Nullam urna nulla, ullamcorper in, interdum sit amet, gravida ut, risus. Aenean ac enim. In luctus. Phasellus eu quam vitae turpis viverra pellentesque. Duis feugiat felis ut enim. Phasellus pharetra, sem id porttitor sodales, magna nunc aliquet nibh, nec blandit nisl mauris at pede. Suspendisse risus risus, lobortis eget, semper at, imperdiet sit amet, quam. Quisque scelerisque dapibus nibh. Nam enim. Lorem ipsum dolor sit amet, consectetuer adipiscing elit. Nunc ut metus. Ut metus justo, auctor at, ultrices eu, sagittis ut, purus. Aliquam aliquam.

ACKNOWLEDGMENTS

So long and thanks for all the fish.

REFERENCES

Albert, Carlo, and Sören Vogel. 2017. *GUTS: Fast Calculation of the Likelihood of a Stochastic Survival Model*. `https://CRAN.R-project.org/package=GUTS`.

Albert, Carlo, Sören Vogel, and Roman Ashauer. 2016. "Computationally Efficient Implementation of a Novel Algorithm for the General Unified Threshold Model of Survival (Guts)." *PLoS Comput Biol* 12 (6). Public Library of Science: e1004978.

Ashauer, Roman, Anita Hintermeister, Ivo Caravatti, Andreas Kretschmann, and Beate I Escher. 2010. "Toxicokinetic and Toxicodynamic Modeling Explains Carry-over Toxicity from Exposure to Diazinon by Slow Organism Recovery." *Environmental Science & Technology* 44 (10). ACS Publications: 3963–71.

Baudrot, Virgile, Sandrine Charles, Marie Laure Delignette-Muller, Wandrille Duchemin, Guillaume Kon-Kam-king, Christelle Lopes, Philippe Ruiz, and Philippe Veber. 2018. *Morse: MOdelling Tools*

for Reproduction and Survival Data in Ecotoxicology. https://cran.r-project.org/web/packages/morse/index.html.

Baudrot, Virgile, Sara Preux, Virginie Ducrot, Alain Pavé, and Sandrine Charles. 2018. "New Insights to Compare and Choose Tktd Models for Survival Based on an Inter-Laboratory Study for *Lymnaea Stagnalis* Exposed to Cd." *Environmental Science & Technology*, no. 52, 3 (January). ACS Publications: 1582–90. doi:10.1021/acs.est.7b05464.

Carpenter, Bob, Andrew Gelman, Matthew D Hoffman, Daniel Lee, Ben Goodrich, Michael Betancourt, Marcus Brubaker, Jiqiang Guo, Peter Li, and Allen Riddell. 2017. "Stan: A Probabilistic Programming Language." *Journal of Statistical Software* 76 (1). Columbia Univ., New York, NY (United States); Harvard Univ., Cambridge, MA (United States).

Delignette-Muller, Marie Laure, Philippe Ruiz, and Philippe Veber. 2017. "Robust Fit of Toxicokinetic–Toxicodynamic Models Using Prior Knowledge Contained in the Design of Survival Toxicity Tests." *Environmental Science & Technology* 51 (7). ACS Publications: 4038–45.

Gabry, Jonah, and Ben Goodrich. 2017. *Rstantools: Tools for Developing R Packages Interfacing with 'Stan'*. https://CRAN.R-project.org/package=rstantools.

Jager, Tjalling, Carlo Albert, Thomas G Preuss, and Roman Ashauer. 2011. "General Unified Threshold Model of Survival - a Toxicokinetic-Toxicodynamic Framework for Ecotoxicology." *Environmental Science & Technology* 45 (7). ACS Publications: 2529–40.

Jager, Tjalling, and Roman Ashauer. 2018. *Modelling Survival Under Chemical Stress. a Comprehensive Guide to the Guts Framework. Version 1.0.* Edited by Leanpud.

Vehtari, Aki, Andrew Gelman, and Jonah Gabry. 2017. "Practical Bayesian Model Evaluation Using Leave-One-Out Cross-Validation and Waic." *Statistics and Computing* 27 (5). Springer: 1413–32.